

## **REMARKS**

### **I. Introduction**

In response to the Office Action dated October 29, 2009, claims 1 and 5 have been amended. Claims 1-8 remain in the application. Reconsideration of the application, as amended, is requested.

### **II. Claim Amendments**

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and do not introduce new matter. Support for the amendments can be found in the application as originally filed as follows.

Support for the amendment to claim 1 can be found in the specification at page 7, lines 15 to 21, and at page 24, lines 6 to 8.

Claim 5 has been amended to make it consistent with the corresponding phrase in claim 1, from which it depends. Support for the amendment to claim 5 can be found in the specification at page 6, line 25.

### **III. Examiner Interview Summary**

Record is made of a telephone interview between Applicants' attorney Karen S. Canady, Dr. Ernest Noble, Examiner Lundgren, and Supervisory Patent Examiner Low. on March 16, 2010, in connection with the present patent application. Discussion during this interview focused on the nature and quality of the data presented in the working examples of the above-identified patent application. Examiner Lundgren requested a Declaration by Dr. Noble clarifying the details of the measurements described in the working examples and the statistical analyses used to evaluate the data. Examiner Lundgren also noted that claim 1 should be amended to include a further step describing the dosing or action taken following the determining step. Applicants appreciate the Examiner's suggestions and guidance and have prepared this Amendment and submitted Dr. Noble's Declaration in a good faith effort to advance prosecution and resolve the remaining issues. Should the examiner find further issues to be resolved in order to place the application in condition for allowance, the courtesy of a telephone call to Applicants' undersigned representative would be most appreciated.

### **IV. New Matter Rejection**

At pages 2-4 of the Office Action, the Examiner maintained the rejection of claims 1, 2, and 5-8 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description

requirement for containing new matter. It is alleged that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant invention, at the time the application was filed, had possession of the claimed invention. The Applicants traverse this rejection for the reasons set forth below. Reconsideration is respectfully requested.

The rejection is based on the erroneous statement (errors indicated with bold type) appearing in the Summary of the Invention at page 2 of the application as originally filed (and in claim 1 as originally filed):

Patients having the Taq1A (A1) allele (A1+ allelic status) are candidates for treatment with **high dose of high D2 dopamine receptor binding** antipsychotics and/or SSRIs that influence D2 dopamine receptor density. Patients lacking the Taq1A allele (A1- allelic status) are not likely to respond well to these SSRIs, and are candidates for treatment with **low dose of low D2 dopamine receptor binding or low dose high D2 dopamine receptor binding** atypical antipsychotics.

The statement noted above would have been readily understood to one skilled in the art upon reading the entire application as filed, at the time of filing, as erroneous in its guidance regarding antipsychotic medications (and not with regard to the antidepressant SSRIs) because it directly contradicts the experimental findings reported in the working examples relating to antipsychotic medications as discussed below. The erroneous portion of this statement is the switching of "high dose" and "high binding" for "low dose" and "low binding" in the first sentence describing the treatment suitable for A1+ patients, and the converse in the second statement.

As detailed in the Declaration by inventor Ernest P. Noble, M.D. Ph.D. submitted herewith, the working examples describe experiments which show that A1+ patients, and not A1- patients, experience more adverse effects with high doses of atypical antipsychotics, or when treated with high DRD2 binding antipsychotics ("typical antipsychotics"; see page 5, lines 1-7 of the specification). Example 1 shows that Risperidone, a high binding antipsychotic, exhibits a significant ( $p=0.028$ ) gene by dose interaction, meaning that A1+ patients experience more severe extrapyramidal side effects at low doses than A1- patients, while the latter group experiences more side effects at high doses. Example 2 shows that A1 allelic status has a significant effect ( $p=0.018$ ) on susceptibility to hyperprolactinemia. The loose binding agent Clozapine, in particular, resulted in significant ( $p=0.04$ ) and more than two-fold higher prolactin levels in A1+ versus A1- patients. It is clear on the basis of the data presented in Examples 1 and 2, therefore, that the statement in the "Summary of the Invention" that A1+ patients are candidates for treatment with high dose of high DRD2 binding antipsychotics was intended to recite "low dose of low DRD2 binding antipsychotics" instead. Examples 1 and 2 show that high DRD2 binding agents (Risperidone and typical antipsychotics) are clearly not advised for A1+

patients, while A1- patients can better tolerate treatment with high binding agents or with high doses of low binding agents without experiencing adverse side effects.

In the telephonic interview noted above, Examiner Lundgren expressed doubts about the strength of the data presented in the working examples, as not all of the differences described reach the level of statistical significance having a  $p$  value of 0.05. Applicants acknowledge that large variability in individual measures, such as the prolactin levels presented in Table 1 at page 21, is common in this art, but respectfully note that where some measures are only trends that fail to reach statistical significance, these trends still support the assertion that one skilled in the art would regard the data in the working examples as contradicting the statement in the Summary of the Invention that A1+ patients are candidates for treatment with high dose of high DRD2 binding antipsychotics. All of the data relating to antipsychotic medications, both those that are statistically significant and those that are not, are consistent with treating A1+ patients with low doses of low DRD2 binding antipsychotics and with treating A1- patients with either high doses (e.g. of the low binder Clozapine) or high DRD2 binders.

The data on SSRIs (antidepressants) are unambiguous in their support for use with A1+ patients and not with A1- patients. As explained in Dr. Noble's Declaration submitted herewith, the data in Example 3 of the specification and presented in Figure 6 show that A1- patients do not exhibit improvement in GHQ scores with SSRI treatment, while A1+ patients show statistically significant improvement in their social dysfunction scores ( $p=0.031$ ) and a strong trend toward improvement in anxiety/insomnia and depression scores. Moreover, the statistically significant difference between A1+ and A1- patients in GHQ scores observed at baseline (see Figure 4; total GHQ and GHQs 2-4) disappears after paroxetine treatment, confirming that paroxetine treatment is beneficial to A1+ patients, but not for A1- patients. Applicants respectfully note, in addition, that this portion of the claim language, relating to which patients are candidates for SSRI treatment, was correct in the application as originally filed, and thus should not be subject to the new matter rejection.

To assist the Examiner, Applicants submit herewith copies of two of the publications based on the work described in the working examples that relate to the data discussed above and in the Declaration by Dr. Noble: Lawford et al. *Eur. Neuropsychopharmacol.* 2003, 13(5): 313-20; and Young et al. *Br. J. Psychiatry* 2004, 185:147-51. Also provided is a copy of the paper by Calarge et al. (*Pharmacogenetics and Genomics* 2009, 12:373-382), referenced in the Declaration, which is an example of confirmatory data subsequently published by another group and citing the work of the inventors. Calarge et al. report that presence of the Taq1AA1 allele is associated with higher prolactin concentration, and that adverse events potentially related to hyperprolactinemia were four times more common in A1 allele carriers.

Neither the data in the working examples, nor in the subsequent published literature, would support the erroneous language in the Summary of the Invention and claim 2 of the application as originally filed. It would have been readily apparent to one skilled in the art that the application teaches that patients positive for the A1 allele are best treated with low doses of low DRD2 binding atypical antipsychotic medications and likely to be harmed by treatment with high doses of high DRD2 binding medications, while A1- patients are the ones who can better tolerate higher doses. Applicants therefore respectfully request the Examiner reconsider and withdraw the new matter rejection.

#### V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

	<p>Respectfully submitted,</p> <p>canady + lortz LLP          4201 Wilshire Blvd., Suite 622          Los Angeles, California 90010          (310) 966-9400          Fax: (909) 494-4441</p> <p>By: <i>/Karen S Canady/</i>          Name: Karen S. Canady          Reg. No.: 39,927</p> <p>Date: March 29, 2010</p>
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